

AWARD NUMBER: W81XWH-14-1-0477

TITLE: Gulf War Illness Inflammation Reduction Trial

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REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 29Sep2016 - 28Sep2017	
4. TITLE AND SUBTITLE Gulf War Illness Inflammation Reduction Trial				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-1-0477	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Ronald R. Bach, PhD E-Mail: Ronald.Bach@va.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Minneapolis VA Medical Center Research Service (151) One Veterans Drive Minneapolis, MN 55417				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The objective of this clinical trial is to find an evidence-based treatment for Gulf War Illness (GWI). Elevated biomarkers of inflammation were observed in our pilot observational study of GWI. Thus, chronic inflammation appears to be part of the underlying pathophysiology of GWI. Reducing GWI-associated inflammation may alleviate some symptom of the disorder and improve the health-related quality of life of veterans with GWI. This is a randomized, two-group, double-blind, placebo-controlled clinical trial of delayed-release prednisone versus matching placebo. A total of 100 veterans with GWI will be enrolled in the trial. Prednisone was chosen as the study drug because of its well-established pleiotropic anti-inflammatory properties. The specific aims of the study are to measure the effects of the treatment on the following: 1) physical and mental functioning 2) pain, fatigue, and cognitive dysfunction 3) biomarkers of inflammation. All regulatory approvals for this clinical trial have been received. Recruitment and enrollment have begun. A successful trial with improved clinical outcomes and reduced proinflammatory biomarkers would be direct evidence of the role that chronic inflammation plays in the underlying pathophysiology of GWI. Thus, a new paradigm for the diagnosis and treatment of GWI would be established. The potential impact of this new paradigm on the health and well-being of veterans with GWI is very significant.					
15. SUBJECT TERMS Gulf War Illness, Chronic Inflammation, Delayed-Release Prednisone					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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Introduction

From August 2, 1990 to July 31, 1991 approximately 697,000 United States military personnel were deployed to the Kuwaiti Theater of Operations during Operation Desert Shield and Operation Desert Storm (Gulf War). Many veterans of this conflict now suffer from an unexplained chronic multi-symptom disorder known as Gulf War Illness (GWI). The symptoms most frequently associated with GWI are widespread pain, unexplained fatigue, and cognitive difficulties. Comprehensive reviews of GWI have been published by the Research Advisory Committee on Gulf War Veterans' Illnesses (1) and the Institute of Medicine (2).

The Department of Veterans Affairs (VA) Office of Public Health has conducted survey studies of the mental and physical health of a population-based cohort of 30,000 Gulf War and Gulf War era Veterans. The most significant health-related difference revealed by these studies was the higher prevalence of unexplained chronic multi-symptom illnesses in the deployed veterans group. Ten years post-deployment the difference was 28.9% vs 15.8% (adjusted odds ratio=2.16) (3). Fourteen years post-deployment the difference was 36.5% vs 11.7% (adjusted risk ratio=3.05) (4). Twenty years post-deployment the difference was 43.9% vs 20.3% (adjusted odds ratio=3.06) (5). Thus, a chronic unexplained multi-symptom illness is the signature health-related outcome of the 1990-1991 Gulf War and the incidence of GWI in the Gulf War veteran population continues to increase.

The absence of information regarding the underlying pathophysiology of GWI has hindered efforts to develop effective treatments. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans with and without multiple symptoms of pain, fatigue, and cognitive dysfunction (6). The goal of the pilot study was to discover a biomarker fingerprint that would identify a potential therapeutic target for the treatment of GWI. Examination to the peripheral blood revealed the biomarker signature of innate immune system activation in veterans with GWI. Thus, chronic inflammation was identified as a potential therapeutic target.

Key Words

Gulf War Illness, Chronic Inflammation, Delayed-Release Prednisone, Evidence-Based Treatment, Clinical Trial, Pain, Fatigue, Cognitive Dysfunction

Accomplishments

1st Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues. Outreach efforts to the Gulf War veteran community were initiated to enhance enrollment and overcome seasonal fluctuations. Details of the efforts are described in Changes/Problems.
- Senator Amy Klobuchar visited the Minneapolis VAMC on February 7, 2017. The purpose of her visit was to receive a briefing from me about our work on Gulf War Illness. The visit was triggered by the Senator's interest in deployment-related illness. This interest is clearly demonstrated by her **Helping Veterans Exposed to Burn Pits Act**. The "Burn Pit" Act has passed the U.S. Senate and is awaiting a vote in the U.S. House of Representatives. I continue to communicate with the Senator and her staff.

2nd Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.
- The results of the pilot study that are the basis for this clinical trial were published in the online journal PLOS ONE (6) on June 23, 2016.
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0157855>
I am delighted to report that there is objective evidence indicating the paper is being widely read. The journal informed us on May 25, 2017 that there have been 15,149 views and 480 downloads of the paper. That puts us in the top 1% most downloaded for all PLOS ONE research articles published in 2016!
- I gave a PowerPoint presentation on GWI at the National Association of State Women Veterans Coordinators 2017 Annual Training Conference.

3^d Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.
- We observed the first evidence that enhanced recruitment methods are having a positive effect. The decline in the running rate of enrollment has reversed.

4th Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues. Additional evidence that enhanced recruitment methods are having a positive effect is observed. For the second straight quarter the running rate of enrollment has increased.

Progress as of 30-09-2017

	# Subjects
Telephone Screen (Kansas Case Definition)	131
Consented/Enrolled	64
Randomized (Passed Safety Screen)	53
Withdrawn	2

	Total Enrollment	Running Enrollment Rate (subjects/month)
09/30/15	11	3.7
12/30/15	16	2.7
03/31/16	24	2.7
06/30/16	29	2.4
09/30/16	40	2.7
12/31/16	41	2.3
03/31/17	47	2.2
06/30/17	54	2.3
09/30/17	64	2.4

Impact

The underlying pathophysiology of GWI is not understood. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans who were GWI- with blood from veterans who were GWI+ (6). The GWI status was determined by the assessment of multiple symptoms of pain, fatigue, and cognitive dysfunction using the CDC 10 survey instrument. The objective of the study was to determine if there are quantifiable differences in blood that could be used to identify potential therapeutic targets for the treatment of GWI. The blood analyses included a complete blood count with differential, plasma proteomics, platelet function studies, and the measurement of multiple coagulation parameters.

The pilot study results provide strong evidence of chronic inflammation in veterans with GWI. This entirely new and provocative line of evidence presents an exciting opportunity to test an intervention that has the potential to both reduce symptoms and further define the pathophysiology of GWI.

The goal of this proof-of-principal trial is to determine if reducing inflammation is an effective treatment for GWI. A successful trial with improved clinical outcomes and reduced biomarkers of inflammation would establish a new paradigm for the diagnosis and treatment of GWI. Evaluating the effects of other anti-inflammatory interventions on clinical outcomes and biomarkers of inflammation in randomized placebo-controlled clinical trials could produce additional improvements in GWI treatment beyond those achieved in this trial. Thus, the immediate and long-term positive consequences for the health and well-being of veterans with GWI would be very significant.

Changes/Problems

Outreach efforts to the Gulf War veteran community aimed at increasing awareness of the Gulf War Illness Inflammation Reduction Trial are underway. Print media, radio programs targeting veterans, and the internet are being employed. Some of the efforts to connect with Gulf War veterans are presented in the following links:

http://www.91outcomes.com/2016_09_01_archive.html
<http://minnesotamilitaryradiohour.com/20160925-gulf-war-illness-minnesota-power>
<http://www.research.va.gov/currents/0716-1.cfm>
<http://www.minneapolis.va.gov/MINNEAPOLIS/research/index.asp>
http://www.eurekalert.org/pub_releases/2016-07/varc-syp071116.php
<http://www.startribune.com/still-sick-25-years-after-the-gulf-war-a-vet-seeks-answers-and-the-minneapolis-va-may-have-them/390138371/>

The initial results of this campaign with respect to enhancing enrollment look promising. Increases were observed in the 3rd and 4th quarters of 2017. We are expanding our effort to increase the rate of enrollment. In the previous quarter the study was posted on the Minneapolis VA intranet and internet sites. The study has also been posted on the "Gulf War Illness" Facebook page. In addition, we are beginning to see a fair number of word of mouth recruits. In this quarter, new VA Research Study Kiosks were installed in the lobby of the Minneapolis VAMC. The flyer for the GWIIRT is located there.

Two additional recruitment enhancement methods were introduced this year. We have reached out to the staff responsible for Veterans affairs in the offices of three Minnesota Congressmen and one Minnesota Senator. Information about the GWIIRT was included in the communication along with a request to have the material distributed to their contacts in the Veterans. In addition, on June 27 I gave a talk on GWI at the National Association of State Women Veterans Coordinators Annual Training Conference. At the conference, I talked with two employees of the state of from Minnesota with established networks of communication within the Minnesota Veteran community. One is the Gold Star Family & Women Veterans Coordinator in the Minnesota Office of Veterans Affairs. The other is in the Director of Military Outreach in State of Minnesota Department of Military Affairs. Both were very interested in what I had to say about GWI and expressed willingness to distribute GWIIRT information to their Gulf War Veterans. The effects of these efforts on recruitment should be evident in numbers presented in the next quarterly report.

On March 25, 2017 I spoke about GWI at the 7th Annual Vietnam Veterans Day festivities at the American Legion Hall in Chippewa Falls, Wisconsin. Gulf War Veterans or their family members were present. Thus, several study subjects were recruited.

Press releases have been issued by VA Office of Research and Development in Washington DC and the Minneapolis VA Health Care System announcing the

publication of our observational study of GWI (see ref 4). We hope the local and national publicity generated by these publications will have a positive effect on enrollment. The following are links to some recent media reports on this clinical trial:

<http://www.research.va.gov/currents/0716-1.cfm>
www.npr.org/2013/03/22/175054277/scientists-search-for-gulf-war-illness-answers
www.research.va.gov/currents/0716-1.cfm
<http://minnesotamilitaryradiohour.com/20160925-gulf-war-illness-minnesota-power>

Products
None

Participants & Other Collaborating Organizations

Name:	Ronald R. Bach, PhD
Project Role:	P.I.
Nearest person month worked:	3
Contribution to Project:	Dr. Bach has overseen the efforts of other study personnel with respect to the regulatory approval process as well as screening, enrollment, and conduct of the study.

Name:	Rebecca Rudquist, BSN
Project Role:	Study Coordinator
Nearest person month worked:	12
Contribution to Project:	Ms. Rudquist has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Name:	Susan Johnson, LPN
Project Role:	Study Staff
Nearest person month worked:	2
Contribution to Project:	Ms. Johnson has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Special Reporting Requirements

None

Appendices

None

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3. Kang HK. Mahan CM. Lee KY. Magee CA. Murphy FM. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. *J Occup Environ Med*. 2000; 42:491-501.
4. Kang HK. Li B. Mahan CM. Eisen SA. Engel CC. Health of US Veterans of 1991 Gulf War: A Follow-Up Survey in 10 Years. *J Occup Environ Med*. 2009; 51:401-410.
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6. Johnson GJ, Slater BCS, Leis LA, Rector TS, Bach RR. Blood Biomarkers of Chronic Inflammation in Gulf War Illness, *PLOS ONE* 2016; 11(6): e0157855. doi:10.1371/journal.pone.0157855.